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ИДИОПАТИЧЕСКИЙ ГИПЕРЭОЗИНОФИЛЬНЫЙ СИНДРОМ. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Idiopathic Hypereosinophilic Syndrome. A Clinical Case

Резюме

Идиопатический гиперэозинофильный синдром является редким феноменом во врачебной практике. Основным критерием диагностики является стойкое повышение уровня эозинофилов выше 1,5*10^9/л в сыворотке крови и отсутствие клинических и лабораторно-инструментальных данных, объясняющих возможную природу данного состояния.

Представлен клинический случай идиопатического гиперэозинофильного синдрома, протекающий под маской острого коронарного синдрома. Детальный разбор данного случая проведен с целью освещения возможного варианта течения данного заболевания, а также для повышения настороженности в области «больших» эозинофилий.

Ключевые слова: *гиперэозинофилия, полиорганная недостаточность, острое нарушение мозгового кровообращения, тромбоэмболия легочной артерии*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Idiopathic hypereosinophilic syndrome is a rare phenomenon in medical practice. The main criterion for diagnosis is a persistent increase in the level of eosinophils above 1.5 * 10^9/ l in the blood serum and the absence of clinical and laboratory and instrumental data explaining the possible nature of this condition.

A clinical case of idiopathic hypereosinophilic syndrome, which occurs under the guise of acute coronary syndrome, is presented. A detailed analysis of this case was carried out in order to highlight a possible variant of the course of this disease, as well as to increase alertness in the area of "large" eosinophilia.

Key words: *hypereosinophilia, multiple organ failure, acute cerebrovascular accident, pulmonary embolism*

Conflict of interests

The authors declare no conflict of interests

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BP — blood pressure, CBC — complete blood count, HR — heart rate, IHES — idiopathic hypereosinophilic syndrome, LV — left ventricle, RR — respiratory rate

The outcome of any disease is largely determined by its timely and correct diagnosis. The difficulties in diagnosing idiopathic hypereosinophilic syndrome (IHES) are caused by the variety of the clinical signs of this disease, however, as well as by the absence of an obvious etiological factor with a clear mechanism for the development of complications. Hematological changes detected during the examination of patient suggest the possible causes of development of the disease and contribute to preventing such development by adjusting the treatment [1].

Eosinophilia in blood serum is not an independent disease, but only its laboratory sign, therefore, it is impossible to predict the specific features of disease course based only on blood test results. However, it is the increase in the number of eosinophils that will narrow the diagnostic search for the causes of disease development [2].

The increased eosinophils in blood serum are primarily associated with the development of an immediate allergic reaction or with persistent helminthiasis. Eosinophil count within 0.6×10^9/L is considered as eosinophilia, and an increase over 1.5×10^9/L — as hypereosinophilia, or "major" eosinophilia [1]. The exclusion of these diseases from the possible eosinophilia causes allows ~~us~~ suspecting other pathologies, including systemic connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis), diseases of gastrointestinal tract (eosinophilic gastritis and colitis), blood diseases (lymphoma, lymphogranulomatosis, Kostmann syndrome), etc. [3].

Hypereosinophilic syndrome is an extremely rare disease. This syndrome is more common in men than in women (9:1). The age of onset is 20-50 years. The clinical presentation is characterized by polymorphism of symptoms and desadaptative changes of body functions [1].

IHES is the diagnosis of exclusion. It is established by a detailed diagnostic search aimed at exclusion of all possible causes of the reactive process and the presence of clonal hypereosinophilia markers.

Case report

Patient N., male, 41; on July 26, 2017 he was delivered by an ambulance team to the admission department of the city clinical hospital with complaints of pressing pain in the region of heart, palpitations, sweating, pronounced weakness.

It is known from the case history that for the first time the patient felt pressing pain in the region of heart a week before the previous hospitalization, due to emotional stress, he relieved the pain by Corvalol drops. He did not seek medical help. The intensity of pain syndrome increased on July 26, 2017; it was accompanied by tachycardia, sweating and weakness in limbs. Self-administration of Corvalol resulted in no effect. He called an ambulance team that transported him to the admission department of the city hospital.

Past medical history: no abnormalities. According to the patient, he had no chronic diseases.

At the time of examination, patient's condition was satisfactory. Clear consciousness. Body mass index 31 kg/m^2. Skin: no rash, moderately pale, wet. Visible mucous membranes: without rash. Palpable lymph nodes are not enlarged, painless, not matted to the skin, underlying tissues and each other. Examination of musculoskeletal, respiratory, cardiovascular and urinary systems revealed no abnormalities. Blood pressure (BP) 130/80 mm Hg on both arms, heart rate (HR) 100 bpm, respiratory rate (RR) 18 per minute. No edemas.

Troponin I blood test of July 26, 2017 — negative.

After the initial therapeutic examination, the patient was admitted to the Cardiology Department with the diagnosis of acute coronary syndrome.

Complete blood count (CBC) results leukocytosis (18×10^9/L), relative lymphopenia (14 %) and eosinophilia (53 %), granulocytes 61.8 %. Blood biochemistry revealed increased concentration of creatinine up to 162 μmol/L (GFR 45 mL/min/1.73 m^2), urea: up to 18.3 mmol/L, glucose: up to 8.4 mmol/L. Common urinanalysis revealed proteinuria (protein 0.52 g/L) and yeast fungi in large quantities.

ECG demonstrated sinus tachycardia with HR of 98 bpm. Left axis deviation. Right bundle branch conduction disorder — widened S wave in I, rSR pattern in V1. Left ventricular (LV) hypertrophy — Sokolow-Lyon index 38 mm. Focal changes on the lower wall cannot be excluded: pathologic Q wave in leads III and AVF, ST segment on flatline, flattened T wave. Repolarisation abnormality along LV lateral wall.

The patient received drug treatment according to the standards of management of patients with non-ST segment elevation acute coronary syndrome: acetylsalicylic acid, clopidogrel, nitroglycerin, heparin, bisoprolol, enalapril, atorvastatin.

Despite the ongoing treatment, on July 31, 2017, the patient's condition deteriorated sharply: there appeared severe headaches with no definite localization, dizziness, increased dyspnea and general weakness. The patient was not ambulant, however, he sat in bed without support. Speech became indistinct. General condition was assessed as severe. Skin was pale, covered with cold sweat. Abdomen was not distended, painless on palpation. In lungs — vesicular breathing, diffusely weakened throughout all lung fields. Heart sounds were muffled, rhythm was regular, no heart murmur heard, BP 110/70 mm Hg on both arms, HR 110 bpm.

The patient was urgently transferred to the intensive care unit.

CBC over time: leukocytosis 23.4×10^9/L; lymphopenia 8.5 %; granulocytes 81.0 %; increased erythrocyte sedimentation rate up to 48 mm/h; eosinophilia persisted at 50 %, with varying degree of maturity: eosinophilic myelocytes — 1 %, immature eosinophils — 2 %, stab eosinophils — 23 %, segmented eosinophils — 24 %. Serum concentrations of urea and creatinine increased to 29.1 mmol/L and 215 μmol/L, respectively, of glucose — up to 13.6 mmol/L. C-reactive protein value was 53.6 mg/L.

Due to build-up of dyspnea, thromboembolism of the small branches of pulmonary artery was suspected. D-dimer serum concentration was 1.0 mg/L at normal range of 0-0.5 mg/L. Coagulation parameters (activated partial thromboplastin time, prothrombin time, Quick prothrombin index, international normalized ratio) were within normal range.

Chest X-ray suggests the embolism of the small branches of pulmonary artery enhanced vascular pulmonary pattern; dilated, poorly structured roots; right hemidiaphragm at the level of the fourth rib; moderately enlarged heart, flattened cardiac arches; venous congestion.

On day 6th after hospitalization, ECG demonstrated persistent sinus tachycardia up to 100 bpm. There were signs of subendocardial ischaemia in the antero-apical-lateral LV region — high T wave in lead I, AVL, V1-V6.

On the same day, due to the onset of the symptoms of motor aphasia and dysarthria, an urgent brain MRI was performed that revealed multiple lacunar infarcts in cerebellum and cerebral hemispheres. During contrast enhanced brain MRI, none of the described foci and meninges accumulated the contrast agent.

The patient was seen by a neurologist and diagnosed with "multiple lacunar infarcts in both hemispheres of brain and cerebellum, probably of atherosclerotic subtype, associated with arterial hypertension, cerebral atherosclerosis."

From July 31 (day 6th after hospitalization), ethylmethylhydroxypidine succinate with antioxidant, antihypoxant and membrane-protective purposes, as well as succinic acid in combination with inosine, nicotinamide and riboflavin as an energy-synthesing agent were added to the ongoing drug therapy. Due to increasing signs of manifest inflammatory process in blood (leukocytosis, leftward shift), ceftriaxone and metronidazole were added to the treatment regimen for antibacterial and anti-inflammatory purposes. In view of the suspected embolism of the small branches of pulmonary artery, aminophylline was prescribed to reduce pressure in the pulmonary artery and facilitate the patient's breathing. Unfractionated heparin followed by enoxaparin sodium were added for antithrombotic purposes.

On August 1, 2017 (day 7th of hospitalization), the patient's condition was assessed as extremely severe. There were negative changes in the form of increased signs of cerebral insufficiency: consciousness was lost, verbal contact was absent. Skin was moderately pale. Spontaneous breathing: vesicular breathing in lungs, weakened in the lower parts, RR 22 per minute. BP 110/70 mm Hg on both arms, HR 120 bpm. No reaction to painful stimulus. There was edema of left lower limb.

Ultrasound examination of the vessels of lower limbs revealed phlebothrombosis of left femoral vein. Thrombectomy of the floating part of the thrombus with phleboplication was immediately performed.

In view of anticoagulants administration, esophagogastroduodenoscopy was performed to exclude erosive and ulcerative lesions of gastrointestinal tract, it identified a duodenal ulcer and Forrest 2B bleeding risk.

Aminocaproic acid and esomeprazole for parenteral administration were added to the treatment. Aminocaproic acid was prescribed to achieve injection hemostasis and to prevent relapse that may occur due to Forrest 2B.

CBC demonstrated persisting significant eosinophilia, leukocytosis, and increased erythrocyte sedimentation rate.

Considering the objective status and the results of laboratory tests and instrumental examinations, the patient's condition on day 7th of hospitalization was regarded as progressive multiple organ failure due to a systemic inflammatory response of an unspecified nature with organic damage of brain (multiple lacunar ischaemic foci), kidneys (necrotizing glomerulonephritis with increasing renal failure), lungs (thromboembolism of the small branches of pulmonary artery with the development of infarction pneumonia); left-sided acute phlebothrombosis. The patient was diagnosed with disseminated intravascular coagulation syndrome, acute

course; duodenal peptic ulcer complicated by gastrointestinal bleeding that was stopped with non-surgical methods.

After a multidisciplinary team meeting, meropenem and dexamethasone i/v were added to the treatment at a dose of 12 mg 2 times a day due to the persisting febrile fever and suspicion of a bacterial nature of the inflammatory process.

On day 8th, the patient's condition continued to deteriorate. Spontaneous Babinski reflex was observed on both sides. There were no meningeal signs. Body temperature increased to 38-39°C. Saturation 92 %. RR 34 per minute, breathing rhythm was regular. Moist rales in large number were heard in lungs. Tachycardia up to 120 bpm. The patient was given artificial lung ventilation.

Sternal puncture was performed for diagnostic purposes. Bone marrow cell differential count: the composition of punctate is polymorphic with a predominance of eosinophilic cells. Granulocytic lineage is preserved. Neutrophil maturation is not impaired. Eosinophilic lineage is significantly expanded from promyelocytes to mature forms. Maturation index of eosinophils was 0.44 (normal value 0.7). Lymphoid, monocytic and plasmacytic lineages are preserved. Erythrocyte lineage is preserved: normoblastic type of erythropoiesis. Megakaryocytic lineage functions with the release of platelets.

In order to exclude parasitic invasion, feces were tested for helminth eggs — the result was negative. Negative IgM and IgG titers to the causative agents of giardiasis, echinococcosis, opisthorchiasis, toxacorosis trichinosis were also obtained. The values of the components of the complement of circulating immune complexes C1g and C3d, antibodies (AT) to double-stranded DNA (anti-dsDNA; 1.06 IU/mL) and AT to single-stranded DNA (anti-ssDNA; 15.6 IU/mL), anti-nuclear AT (8-AT, ANA-Screen; 0.42 points), antineutrophilic antibodies (ANCA screen: antigens PR3, MPO; 0.2 points) were within the acceptable range.

Lumbar puncture performed on day 9th of hospitalization (August 3, 2017) revealed an insignificant erythrocyte sediment; protein 0.30 g/L; glucose 5.5 mmol/L; Pandy's test is negative.

Echocardiography (doppler Echo CG) revealed ultrasound signs of LV hypertrophy. Hepatosplenomegaly was diagnosed based on the results of the ultrasound of abdominal organs.

Ultrasound of the vessels of lower limbs over time (August 4, 2017) revealed thrombosis of great saphenous vein, deep veins of lower leg, popliteal vein. The patient continued receiving the infusion of enoxaparin sodium at a dose of 0.4 ml 2 times a day.

Leukocytosis with significant eosinophilia persisted until August 5 (day 11th in the hospital). Lymphocyte count normalized. Anemia and thrombocytopenia gradually increased, and on August 9, hemoglobin value was 84 g/L, RBC 2.70×10^{12}/L and platelet count 80×10^{9}/L. The concentration of urea and creatinine over time (day 15) was 36.4 mmol/L and 459 μmol/L, respectively. The patient was diagnosed with acute kidney injury of prerenal type.

On ECG, sinus tachycardia and ischaemia in the inferior and antero-apical- posterior regions of the LV persisted.

The patient's condition continued to deteriorate, on August 8th, 2017 (day 14th) was regarded as extremely severe: the patient didn't open his eyes, did not fix his gaze. There were no active movements in limbs. The skin was pale, moist to the touch. Body temperature was 38.3°C. Breathing through the endotracheal tube. Breathing in lungs was heard from both sides. During the irrigation of tracheobronchial tree, purulent sputum with streaks of blood was observed. Regular heart rhythm on auscultation, muffled heart tones. BP 130/70 mm Hg, RR 120 bpm. Abdomen was not distended and did not respond to palpation. No edema of lower limbs.

Considering the available data, on August 9th, 2017 (day 15), based on the results of clinical examinations and laboratory tests, as well as on the exclusion of probable etiological factors, the patient was diagnosed with "idiopathic hypereosinophilic syndrome with multiple organ damage."

Doppler Echo CG on day 15 revealed a small amount of fluid in pericardium. Ultrasound of abdominal organs demonstrated hepatosplenomegaly, diffuse focal changes in spleen and liver, and signs of intestinal paresis.

On August 9, at 02:30 p.m. the patient had cardiac arrest. 30 minutes of resuscitation measures with no effect. Biological death was confirmed at 03:00 p.m.

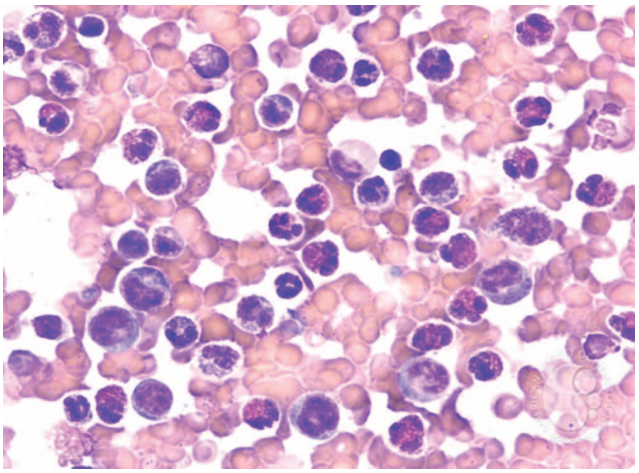

Figure 1. *Microscopic preparation for idiopathic hypereosinophilic syndrome*

Note: for illustration of clinical case, source: URL: https://ru.techsymptom.com/50355-hypereosinophilic-syndrome-92 (date of the application: 14.07.2022)

Extract from the autopsy protocol (August 09, 2017). IHES. Disseminated intravascular coagulation involving heart, brain, spleen and kidneys. Multiple cerebral infarcts, non-coronary foci of myocardial necrosis. Vein thrombosis of left lower limb. Embolism of the small branches of pulmonary arteries. Hemorrhagic infarction in the middle lobe of right lung. Ulcer of duodenal bulb. Left-sided phleboplication (Figure 1).

Discussion

Eosinophilia develops in connection with many diseases; however, the number of eosinophils should not exceed 5-10 % of the total number of WBC [1].

"Major" eosinophilia is extremely rare, its etiological factor is often unknown, and its pathogenesis is unclear. The most illustrative examples of pronounced hypereosinophilia include: Churg-Strausssyndrome that includes severe bronchial asthma with hypereosinophilia, eosinophilic infiltrates, necrotizing eosinophilic vasculitis and granulomas in different organs [2] and IHES.

In the presented clinical case, the patient had no bronchial asthma or maxillary sinus pathology, there was no data on the history of neuropathy what made it possible not to stop on the diagnosis of Churg-Strauss syndrome, but to suspect IHES.

IHES was first described in 1968 by W. Hardy et al. [3], and in 1975 M. Chusid et al. identified three typical features of this syndrome [4]:

1) peripheral blood hypereosinophilia that persists for at least 6 months (more than 1,500 cells/μL or more than 37 % of the total number of all WBC);
2) no other causes for eosinophilia;
3) changes in organs or their functions associated with eosinophilia.

Literature sources describe sporadic clinical cases of IHES that manifested as endocardial fibroelastosis, encephalopathy, peripheral neuropathy, transient ischemic attacks, eosinophilic infiltrates in lungs, hepatitis [1].

In IHES, hematological syndrome occurs in 100 % of patients, cardiac damage — in 58 %, skin manifestations — in 56 %, pulmonary syndrome — in 49 %, hepatic damage — in 30 %, gastrointestinal symptoms — in 23 % [5–7].

In the presented clinical case, the patient had severe eosinophilia (more than 50 % of the total number of

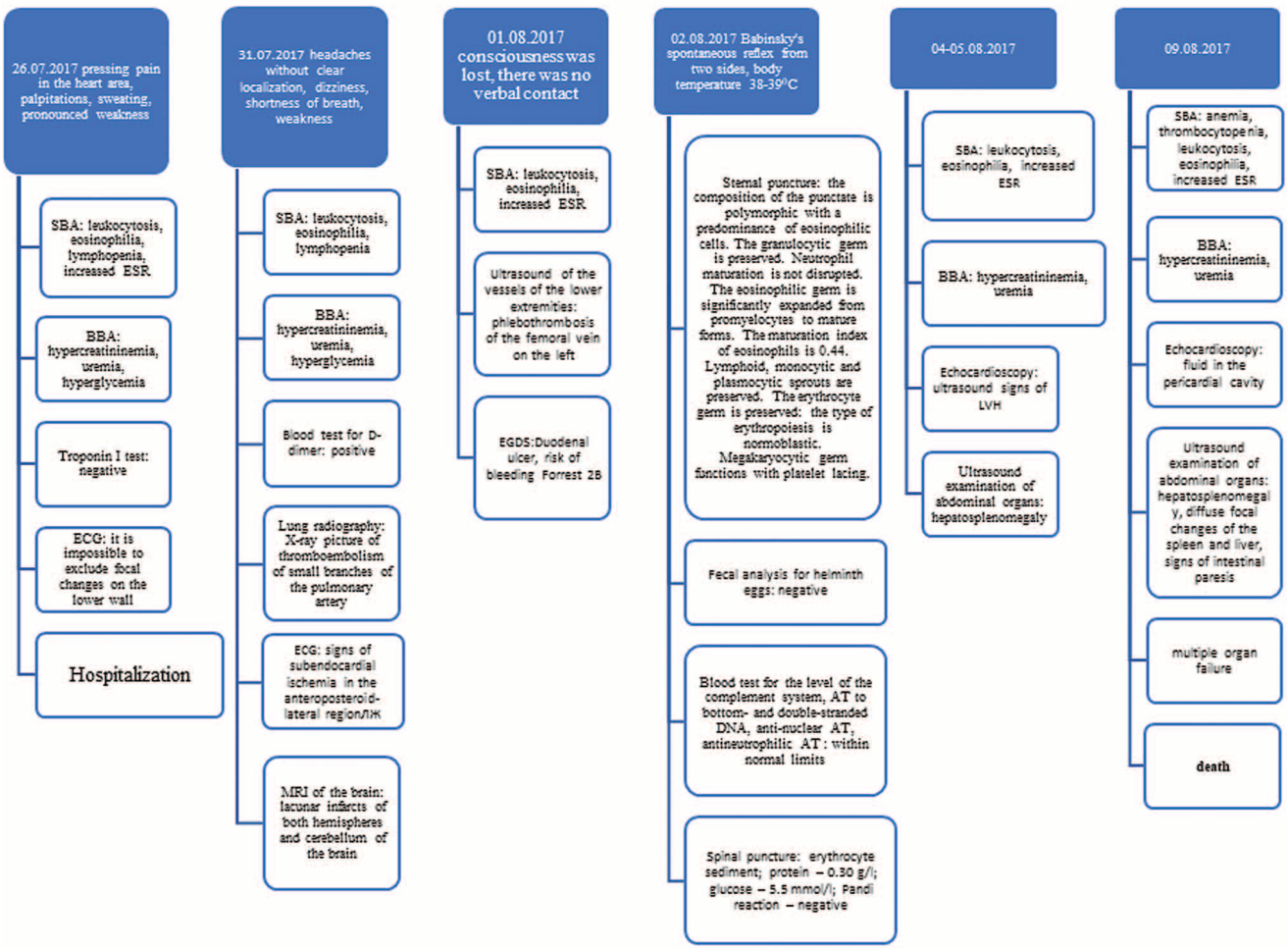

Figure 2. *Chronology of the course of the disease*

WBC) what corresponds to the IHES criteria. The patient's clinical presentation started with the development of eosinophilic myocarditis that was considered as an acute coronary syndrome. During the next three days, the following also developed: acute impairment of cerebral circulation — damage to central nervous system, thromboembolism of the small branches of pulmonary artery and atelectasis of the right lung — pulmonary syndrome, duodenal ulcer complicated by bleeding — gastrointestinal syndrome. Later, there were floating thrombi in the vessels of lower limbs, signs of acute renal failure caused, with underlying IHES, by necrotizing glomerulonephritis, i.e. renal syndrome. By day 7 of hospitalization, the patient developed disseminated intravascular coagulation syndrome.

According to the results of CBC and sternal punction, no convincing data were found for a blood disease what allowed excluding hematological diseases from the possible etiological factors in the development of hypereosinophilia. Since all obvious causes of hypereosinophilia were excluded during the diagnostic search, the final clinical diagnosis was IHES.

Despite intensive drug therapy, the patient developed fatal multiple organ failure that led to death.

Thanatogenesis in this pathology is based on the imbibition of the tissues of heart, brain, spleen, kidneys and blood vessels by eosinophils. Upon death, eosinophils secrete cationic proteins and eosinophilic neurotoxins with bactericidal activity; they stimulate histamine release by mast cells that causes desquamation of healthy epithelial and endothelial cells [5]. The processes described were observed in the patient in the presented clinical case.

In this case, the disease was characterized by a rapidly progressive course with no positive changes in response to the treatment. The clinical presentation of IHES is always complex and unpredictable. However, we would like to pay special attention to the initial clinical symptoms of the disease: its primary sign was the ACS. Although cardiac damage in IHES develops in 58 % of cases [5], it most often occurs under the "mask" of inflammatory myocardial damage. Disease onset in most cases is manifested by skin and articular syndromes. A specific feature of this case that requires the attention of practitioners is the ACS-type heart disease that further complicated differential diagnosis and, possibly, affected the outcome of the disease.

Conclusion

The presented clinical case draws the clinicians' attention to the existence of "major eosinophilia" and the need for its differential diagnosis and management. Alertness and awareness of the idiopathic hypereosinophilic syndrome in clinical practice will help to timely identify this disease and prevent the development of life-threatening complications.

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